Case Report

Combination therapy with radiation and hyperthermia-induced clinical complete response of small cell carcinoma of prostate

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Abbreviations & Acronyms
CR = complete response
CT = computed tomography
GS = gleason's score
Hsp70 = heat shock protein 70
HT = hyperthermia
MRI = magnetic resonance imaging
NSE = neuron-specific enolase
ProGRP = pro-gastrin-releasing-peptide
PSA = prostate-specific antigen
RT = radiation therapy
SCCP = small cell carcinoma of the prostate

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How to cite this article: Kawai N, Nagai T, Naiki-Ito A *et al*. Combination therapy with radiation and hyperthermia-induced clinical complete response of small cell carcinoma of prostate. *IJU Case Rep*. 2022; **5**: 113–116.

Received 21 July 2021; accepted 30 November 2021.
Online publication 14 January 2022

Introduction: Small cell carcinoma of the prostate has a poor prognosis even with standard systemic chemotherapy. We report a case, in which combination therapy with radiation and hyperthermia-induced clinical complete response.

Case presentation: An 87-year-old man complaining of dysuria was referred to our hospital. Based on magnetic resonance imaging findings and a history of prostate cancer, a prostate biopsy was performed, and small cell carcinoma of the prostate was diagnosed. Whole-pelvis radiation therapy was administered with an additional dose to the prostate; eight cycles of hyperthermia treatment (8 MHz radiofrequency capacitive regional hyperthermia) were administered concurrently. Normalized neuron-specific enolase levels and magnetic resonance imaging confirmed a complete response. A few cancer cells were seen in the post-treatment biopsy specimen, which demonstrated positive immunostaining for heat shock protein 70 and HIKESHI.

Conclusion: In this case, small cell carcinoma of the prostate was effectively treated with combined radiation and hyperthermia therapy.

Key words: clinical complete response, combination therapy, hyperthermia, radiation, small cell carcinoma of prostate.

Keynote message

Small cell carcinoma of the prostate accounts for less than 2% of prostatic primary tumors. It is rarely detected and has a poor prognosis. Our findings suggest that combination therapy with radiation and hyperthermia may offer therapeutic benefits for these carcinomas.

Introduction

SCCP is a rare tumor, accounting for 0.5–2% of patients with prostate cancer.[1] Since small cell carcinomas are aggressive in nature and are often only diagnosed in the later stages, the median survival time for patients is short, with an average of 8–16 months.[2] In February 2019, the National Comprehensive Cancer Network published new clinical practice guidelines stating that, regardless of the stage at initial presentation, SCCP should be managed with cytotoxic chemotherapy such as cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, or by participation in clinical trials.

Here, we report a case in which combination therapy using radiation and HT, instead of chemotherapy, induced a clinical CR in SCCP.

Case presentation

An 87-year-old Japanese man presented to our department with urinary retention. Six years previously, he had been diagnosed with prostate cancer (GS 4 + 4 and cT2aN0M0). He was treated with androgen deprivation therapy for 6 years, and his PSA level was below the measurement sensitivity of 0.003 ng/mL.

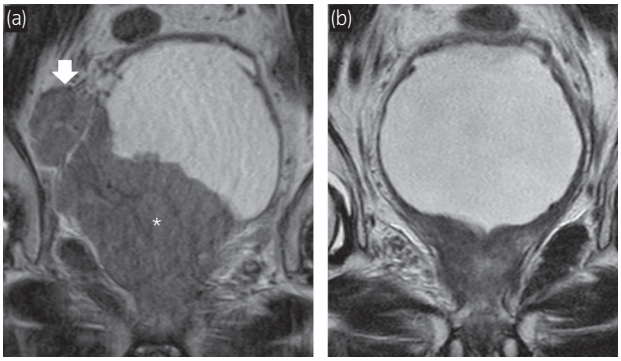

Fig. 1 Magnetic resonance images of the right obturator lymph node. (a) MRI on referral to our hospital. The white arrow indicates the right obturator lymph node. The asterisk indicates the point at which prostate cancer has invaded the bladder. (b) After treatment. The carcinoma is no longer visible and the prostate has shrunk to a normal size.

CT and MRI revealed a relapse of prostate cancer with bladder invasion and right obturator lymph node metastasis without distant metastases (Fig. 1a). Pathological findings of a transperineal ultrasound-guided prostatic biopsy showed small cell carcinoma immunoreactivity for the neuroendocrine markers synaptophysin, chromogranin A, and CD56 (Fig. 2a–e).

As the patient refused the standard treatment of chemotherapy for SCCP, he was administered whole-pelvic RT using 10 MV high-energy linear accelerators (44 Gy/2 fr), with an additional dose (16 Gy/8 fr) administered to the prostate with palliative intent to relieve urinary retention. RT was delivered using a four-field box technique. Concurrent 8-MHz radiofrequency capacitive regional HT was administered concurrently using a Thermotron RF-8 (Yamamoto Vinita Co., Osaka, Japan) for the purpose of sensitizing the effect of RT. HT was administered once weekly for 15 mins' irradiation. The patient underwent eight cycles of HT treatment targeting the prostate.

MRI performed after treatment revealed that the right external iliac lymph node had disappeared. In addition, the prostate, which had shown bladder infiltration, also shrank to normal size. These findings indicated clinical CR (Fig. 1b). After treatment, he could void without a urethral catheter, and NSE levels decreased from 91.9 ng/mL before treatment to 16.0 ng/mL (below normal range) after treatment (Fig. 3).

To evaluate the therapeutic effect, a needle biopsy of the prostate was performed after the completion of RT (five HT sessions). Pathological findings revealed that only a few cancer cells remained in the biopsy specimens. These remaining cancer cells demonstrated positive staining for chromogranin A, synaptophysin (Fig. 2f–j), HSP70, and HIKESHI (Fig. 4). No new lesions were observed 6 months after the treatment.

Discussion

As the present patient strongly refused chemotherapy, the standard therapy for SCCP, combined therapy with radiation and HT was proposed as an alternative. One of the reasons for this proposal was the presence of a report, that suggested that external beam RT administered concomitantly with platinum-based chemotherapy appears to offer the best survival outcomes for patients with limited or locally advanced disease.[3] The other reason for this proposal was that HT, which increases the temperature in cells and tissues using heating methods such as electromagnetic therapy to offer an antitumor effect, has a sensitizing effect on RT.

HT is a treatment method covered by insurance in Japan, as electromagnetic wave HT for deep-seated malignant tumors. Prospective studies have shown it to be effective in the treatment of pancreatic, colon, and uterine cancers among others, in combination with anticancer agents and RT.[4–8] Since urological cancer is basically removed by surgery, HT treatment itself is not popular among urologists. However, HT combined with chemotherapy is considered a promising approach to cancer therapy.[9,10] A combination therapy of definitive RT and HT has demonstrated prolongation of biological disease-free survival in high-risk and very high-risk prostate cancer patients.[11] A number of elementary studies on the anti-cancer effects of HT show that it causes protein and lipid degeneration, deoxyribonucleic acid double-strand breaks,[12] and changes in signal transduction systems.[13] There have also been interesting reports on how it affects the cell cycle.

Cancer cells are generally quite sensitive to radiation in the M phase and resistant to it in the S phase. The heat

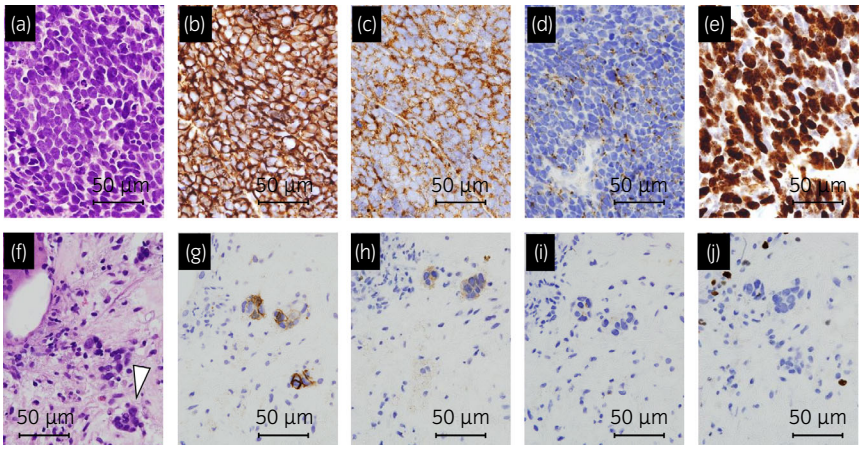

Fig. 2 Pathological findings before and after treatment. (a–e) Specimens before treatment. (a) HE stain, (b) CD56, (c) synaptophysin, (d) chromogranin A, (e) Ki67. (f–j) Specimens after treatment. (f) HE stain, (g) CD56, (h) synaptophysin, (i) chromogranin A, (j) Ki67. HE staining after radiation and HT therapy. Almost all cancer cells have disappeared. The white triangle indicates the few remaining cancer cells. (d–g) The few remaining cancer cells demonstrated positive immunostaining for (g) CD56, (h) synaptophysin, (i) chromogranin A, and (j) Ki67.

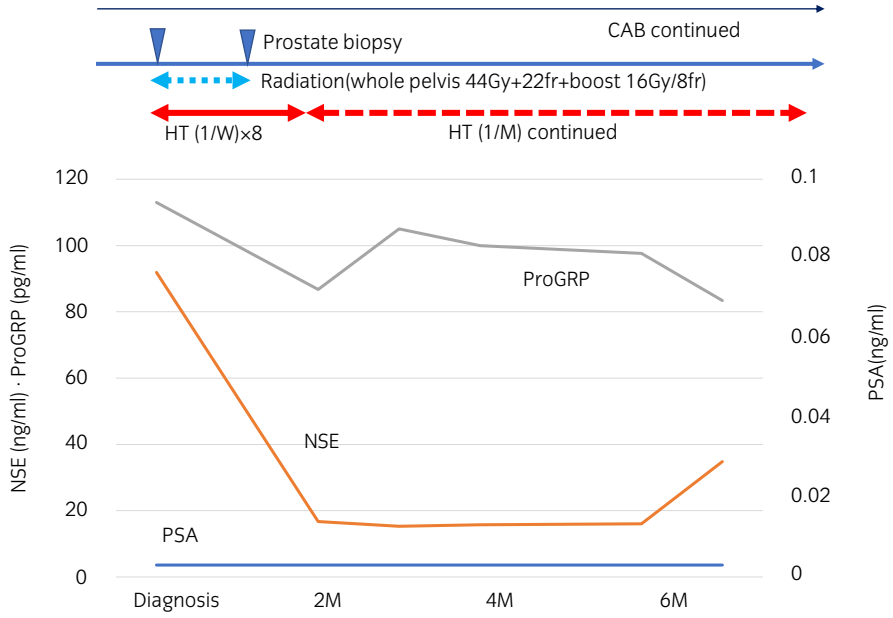

Fig. 3 Longitudinal change of the serum PSA level, NSE, ProGRP. The treatment schedule is indicated. PSA levels were below 0.003 ng/mL before the start of treatment and continued. NSE levels dropped significantly after the start of treatment.

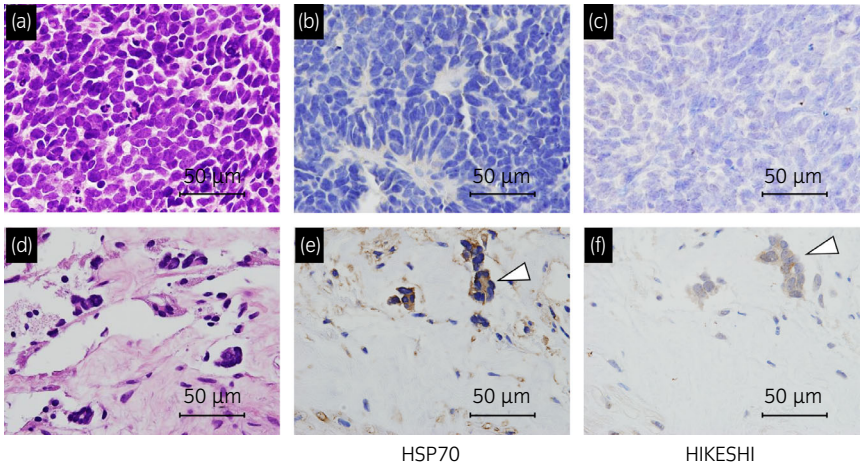

Fig. 4 Immunostaining for Hsp70 and HIKESHI before and after treatment. (a–c) HE, Hsp70, and HIKESHI staining before treatment, respectively. Active staining was demonstrated for neither Hsp70 nor HIKESHI. (d–f) HE, Hsp70, and HIKESHI staining after treatment, respectively. Positivity was observed for both, Hsp70 and HIKESHI (white arrow).

sensitivity of cancer cells is also associated with the cell cycle: cancer cells heated in the S phase show greater sensitivity. When a combination of HT and RT is applied to cancer cells in the S-phase, HT effectively enhances the sensitivity of cancer cells to radiation.[14] Although the effect of combination therapy on the cell cycle was not examined in this case, this mechanism may have resulted in the clinical CR observed in this patient.

Hsp70 and HIKESHI were detected in the remaining cancer cells. Hsps are a group of proteins, that are induced and synthesized when cells respond to stress. These proteins can, therefore, be considered endogenous cytoprotective factors.[15] When cells are exposed to stress, such as heat, Hsp70 is rapidly transported from the cytoplasm to the nucleus. At this time, it is transported intranuclearly by a transporter receptor called HIKESHI,[16] which may be a novel target gene for HT in the future, as blocking HIKESHI enhances the therapeutic effect of HT.[17]

Author Contributions

Noriyasu Kawai: Conceptualization; Writing – original draft; Writing – review & editing. **Takashi Nagai:** Data curation; Writing – review & editing. **Aya Naiki-Ito:** Data curation; Investigation; Writing – review & editing. **Keitaro Iida:** Data curation; Writing – review & editing. **Toshiki Etani:** Data curation; Writing – review & editing. **Taku Naiki:** Data curation; Writing – review & editing. **Shuzo Hamamoto:** Data curation; Writing – review & editing. **Atsushi Okada:** Data curation; Writing – review & editing. **Taro Murai:** Conceptualization; Data curation; Writing – review & editing. **Takahiro Yasui:** Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

This article was approved by the Nagoya City University Graduate School of Medical Sciences Institutional Review Board (#60-21-0026).

Informed consent

Written informed consent was obtained from the patient for publication of this article and accompanying images and is available for review by the Editor-in-Chief.

Registry and the Registration No. of the study/trial

N/A.

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Editorial Comment

Editorial Comment to Combination therapy with radiation and hyperthermia-induced clinical complete response of small cell carcinoma of prostate

Small cell carcinoma of the prostate (SCCP) is usually treated with chemotherapy, such as cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, and participation in clinical trials. However, it would be difficult to introduce chemotherapy in elderly patients and patients who have other diseases that affect chemotherapy, such as renal dysfunction and heart failure. The authors reported their experience on whole-pelvic radiation therapy with an additional dose administered to the prostate and concurrent 8-MHz radiofrequency capacitive regional hyperthermia for sensitizing the effect of radiation therapy for an 87-year-old man with SCCP.[1]

As other modalities of hyperthermia for prostate cancer, high-intensity focused ultrasound (HIFU) has been used for whole-gland[2] and focal therapies.[3] HIFU is an extracorporeal ablative technology that delivers ultrasonic energy to pinpoint the foci only millimeters wide, and only minor temperature changes from 70 to 98.6°C are observed in the focal zone.[3,4] The 8-MHz radiofrequency capacitive regional hyperthermia warms the wide part sandwiched between electrodes to 42°C. Due to the present case having bladder invasion and right obturator lymph node metastasis of SCCP, radiofrequency hyperthermia was appropriately used due to the wide heat effect around the prostate. The safety of the surrounding large abdominal vessels during the radiofrequency hyperthermia[5]